Citation:

Davison K, Coates AM, Buckley JD, Howe PR. Effect of cocoa flavanols and exercise on cardiometabolic risk factors in overweight and obese subjects. *Int J Obes (Lond)*. 2008 Aug;32(8):1289-96. Epub 2008 May 27.

PubMed ID: 18504447

Study Design:

Randomized Controlled Trial

Class:

A - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

NEUTRAL: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

- To investigate whether cocoa flavanol consumption can improve cardiometabolic function and ultimately body composition in an overweight/obese population.
- To determine whether the addition of a moderate exercise program may enhance the impact of such effects on adiposity.

Inclusion Criteria:

- Males and females
- Sedentary (not exercising >1 per week for the purpose of improving health)
- Ages 18-65
- Body mass index (BMI) > 25 kg/m^2
- Recruited from the general public

Exclusion Criteria:

- People with habitually high cocoa consumption (daily consumption of dark chocolate or >26g milk chocolate or powdered cocoa)
- Stage 2 hypertension [resting systolic blood pressure (SBP)> 160 mm Hg or diastolic BP (DBP) >100 mmHg]
- Existing cardiovascular disease or taking any cardiovascular medications (including aspirin) or fish oil

Description of Study Protocol:

Recruitment

Initial screening for suitability to participate was based on diet and lifestyle questionnaires, measurement of height, weight and blood pressure (BP), and a medical clearance for exercise based on electrocardiogram monitoring during a graded submaximal treadmill test.

Design

Randomized, double-blind, placebo-controlled, parallel, 2x2 factorial design incorporating consumption of cocoa beverages and regular exercise

Blinding used (if applicable): double-blind

Intervention (if applicable)

- Volunteers were block-matched into two groups according to BMI, gender, age and blood pressure (BP). The groups were then randomized to the daily consumption of either a high-flavanol cocoa (HF) or low-flavanol cocoa (LF; placebo) drink for 12 weeks.
- Volunteers in each of the two groups were then further randomized to either undertake a program of regular modest exercise for 12 weeks, or to remain sedentary.
- At baseline (week 0), subjects attended the clinic following an overnight fast (≥12h) for collection of blood samples and measurement of BP, Flow-Mediated Dilatation (FMD), body composition [dual-energy X-ray absorptiometry (DXA)] and fat oxidation during submaximal exercise.
- Each subject then consumed a single packet of the appropriate beverage product (LF or HF; acute intervention) and FMD was reassessed 2 hours later.
- On the day following the baseline testing, subjects commenced the chronic (12-week) intervention and the baseline tests were repeated after 6 and 12 weeks.
- Body composition was assessed at baseline and week 12 only.
- On test days at week 6, cocoa drinks were not consumed until all assessments had been completed.
- Subjects were instructed not to change their dietary habits during the study, aside from consuming the appropriate drink, restricting caffeine intake to no more than two caffeinated beverages per day and avoiding red wine and dark chocolate throughout the intervention.
- Volunteers randomized to undertake regular exercise walked or jogged three times per week for 45 minutes at an exercise intensity that elicited 75% of their age-predicted maximum heart rate (220-age in years) for 12 weeks.
- Nonexercising volunteers were asked to maintain their normal levels of physical activity.
- To assist with maintaining compliance, subjects in the exercise group were required to attend at least one supervised exercise session per week and to maintain a training diary.

Statistical Analysis

- Analysis of variance (ANOVA) with repeated measures was used to determine the effect of the treatments, time of measurement and their interactions on the dependent variables.
- Where ANOVA showed no interaction effect between exercise and cocoa, factorial analysis was performed for each of these separate treatments to detect independent effects.
- Where ANOVA showed a statistically significant main effect, pair-wise comparisons were performed using Tukey's Honestly Significant Differences test to determine differences between means.
- To optimize the analysis of differences between treatments, where appropriate, a nested ANOVA design was used to examine changes in dependent variables from baseline with the treatment factor (cocoa or exercise) nested in time.
- Statistical significance was set at an a level of 0.05.

Data Collection Summary:

Timing of Measurements

- At baseline (week 0), subjects attended the clinic following an overnight fast (≥12h) for collection of blood samples and measurement of BP, flow-mediated dilatation (FMD), body composition [dual-energy X-ray absorptiometry (DXA)] and fat oxidation during submaximal exercise.
- On the day following the baseline testing, subjects commenced the chronic (12-week) intervention and the baseline tests were repeated after 6 and 12 weeks.
- Body composition was assessed at baseline and week 12 only.
- On test days at week 6, cocoa drinks were not consumed until all assessments had been completed.

Dependent Variables

- Endothelial function was assessed by flow mediated dilatation (FMD).
  - The diameter of the brachial artery was measured by a single operator with the use of two-dimensional B-mode ultrasound.
  - Images of the artery were taken before cuff inflation, 10s before cuff release, 10s after cuff release and then every 30s for an additional 3 min
- Resting blood pressure and heart rate were measured after 10 min lying supine by automated oscillometry using a Spacelabs ambulatory BP monitor
  - Four readings were taken over a 15 min period, the first value was discarded and BP was calculated as the mean of the remaining three measurements.
- Body composition was assessed at weeks 0 and 12 only using DXA
  - Abdominal fat content was determined using regional analysis of the body segment bordered superiorly and inferiorly by the lowest point of the rib cage and the uppermost aspect of the iliac crests, respectively, and extended laterally to the outer edge of the rib cage
- Fat oxidation during exercise was assessed at weeks 0, 6 and 12 by indirect calorimetry
- Fasting blood samples were obtained by venipuncture and plasma was stored at -80°C until analysis
  - Fasting plasma glucose and lipid concentrations were determined using a commercial assay kit
  - Fasting plasma insulin concentrations were determined by radioimmunoassay
  - Insulin resistance was estimated from fasting glucose and insulin concentrations using the modified homeostasis model assessment of insulin resistance (HOMA2)

Independent Variables

- High flavanol versus low flavanol cocoa drink
- Regular exercise versus normal levels of physical activity for nonexercising volunteers

Control Variables

Description of Actual Data Sample:

Initial N: 98 subjects were screened; 65 overweight/obese volunteers were enrolled

Attrition (final N): 49 completed the full 12 weeks of the intervention

- 14 withdrew because of time restrictions or changes in personal circumstance unrelated to the requirements of the intervention
- 2 subjects were excluded due to noncompliance with study requirements (1 failed to comply with exercise protocol and 1 went on a calorie restricted diet)
- The other 33 are not accounted for

Age:

	LF+Ex	HF+Ex	LF-Ex	HF-Ex
Number (M/F)	4/9	6/7	3/8	4/8
Age (years)	45.2±3.0	45.5±4.0	44.4±4.4	45.3±4.4

Ethnicity: not described

Other relevant demographics: none described

Anthropometrics

	LF+Ex	HF+Ex	LF-Ex	HF-Ex

Number (M/F)	4/9	6/7	3/8	4/8
Height (cm)	168.7±2.7	168.7±2.9	165.3±4.1	171.5±3.6
Weight (kg)	94.7±2.2	94.7±5.2	94.6±6.1	97.2±5.8
BMI (kg/m^2)	33.5±1.1	33.2±1.6	34.5±1.8	32.8±1.1
Waist (cm)	107±2.0	105±6.0	109±4.0	107±4.0

Location: South Australia

Summary of Results:

Key Findings

- FMD increased significantly in the HF group compared to LF 2 hours after consuming a single 450mg dose of the cocoa drink (P=0.02)
- FMD increased significantly at Weeks 6 and 12 relative to baseline in the HF group compared to LF (P=0.002, cocoa x time interaction)
- Chronic consumption had a sustained effect on FMD which was still evident at least 12 hrs after consumption of the previous dose.
- BP and HR measurements tended to decrease over time with HF compared to LF treatment, although the differences between measurements were not significant at either 6 or 12 weeks.
- The effects at both the time points were taken into consideration by nesting the effects of cocoa on BP in time.
- This combined analysis revealed a significant reduction in both diastolic (P=0.04) and mean arterial pressure (P=0.05) with HF versus LF.

	LF+Ex	HF+Ex	LF-Ex	HF-Ex
Number	13	13	11	12
BMI (kg/m^2)	0.2±0.6	0.5±0.8	0.9±0.4	-0.4±0.6
Waist (cm)	0±0.2	0.2±0.2	0.3±0.2	-0.3±0.2
FMD (%)	-0.4±0.77	1.5±0.68	-0.3±0.53	1.8±0.89
SBP (mmHg)	-0.5±2.3	1.1±1.6	4.2±2.6	-1.9±1.9
DBP (mmHg)	-0.2±1.5	-0.5±1.0	2.8±1.7	-1.8±1.5
HR (bpm)	1.1±2.1	-3.2±1.2	0.1±1.3	-0.1±2.1
Total Chol (mmol^{-1})	-0.56±0.20	-0.42±0.21	-0.28±0.23	-0.16±0.25
LDL Chol (mmol^{-1})	-0.11±0.08	-0.15±0.09	2.02±0.09	-0.08±0.05
HDL Chol (mmol^{-1})	-0.31±0.12	-0.27±0.22	-0.31±0.15	-0.15±0.24
Trigs (mmol^{-1})	-0.17±0.14	-0.02±0.07	0.09±0.13	0.10±0.10
Glucose (mmol^{-1})	0.23±0.14	-0.03±0.08	-0.12±0.12	-0.23±0.93
Insulin (μUml^{-1})	0.82±1.3	-3.5±1.7	0.79±1.34	-1.4±2.7
HOMA2-IR	0.14±0.17	-0.41±0.22	0.08±0.17	-0.21±0.34
Fat Oxid (g min^{-1})	0.062±0.033	0.140±0.042	-0.022±0.024	-0.042±0.043
%BF (%)	-0.46±0.38	-0.42±0.34	0.051±0.26	0.11±0.29
%ABF (%)	-0.52±0.28	-1.31±0.49	-0.06±0.34	0.43±0.32

Other Findings

- Exercise was independently associated with a significant reduction in abdominal body fat percentage (P=0.02)
    - Nesting the effects of cocoa in time revealed a significant improvement in all HOMA2 parameters with HF compared to LF
- This difference in HOMA2 parameters remained when differences at baseline were controlled for using analysis of covariance (P>0.05)

Author Conclusion:

- Although HF consumption was shown to improve endothelial function, it did not enhance the effects of exercise on body fat and fat metabolism in obese subjects.
- However, it may be useful for reducing cardiometabolic risk factors in this population

Reviewer Comments:

- *Small numbers of subjects in groups*
- *No limitations were mentioned in the discussion of this paper*
- *Subjects not well described*
- *Withdrawal methods were described in the paper but 33 subjects were unaccounted for*
- *Mars Inc is the sponsor so it is unclear if there is any conflict of interest*

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions		
1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	Yes
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	Yes

Validity Questions		
1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	???
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	???
2.4.	Were the subjects/patients a representative sample of the relevant population?	???
3.	**Were study groups comparable?**	Yes
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	Yes
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	Yes
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	Yes
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	N/A
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	???
4.1.	Were follow-up methods described and the same for all groups?	Yes
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	Yes
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	No
4.4.	Were reasons for withdrawals similar across groups?	???
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	Yes

	5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	Yes
	5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
	5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	N/A
	5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
	5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**		Yes
	6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	Yes
	6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	N/A
	6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	Yes
	6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	Yes
	6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	Yes
	6.6.	Were extra or unplanned treatments described?	Yes
	6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	Yes
	6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**		Yes
	7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
	7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
	7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	Yes
	7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
	7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
	7.6.	Were other factors accounted for (measured) that could affect outcomes?	Yes
	7.7.	Were the measurements conducted consistently across groups?	Yes
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**		Yes
	8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
	8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
	8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
	8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	Yes
	8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	Yes
	8.6.	Was clinical significance as well as statistical significance reported?	Yes
	8.7.	If negative findings, was a power calculation reported to address type 2 error?	N/A
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**		???
	9.1.	Is there a discussion of findings?	Yes
	9.2.	Are biases and study limitations identified and discussed?	No
10.	**Is bias due to study's funding or sponsorship unlikely?**		???

10.1.	Were sources of funding and investigators' affiliations described?	Yes
10.2.	Was the study free from apparent conflict of interest?	???